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(71) Applicant: **ABBOTT LABORATORIES**
One Abbott Park Road
Abbott Park, Illinois 60064-3500(US)

(72) Inventor: **Adjei, Akwete L.**
38770 Red Oak Terrace
Wadsworth, Illinois 60083(US)
Inventor: **Kesterson, James W.**
1417 Bullcreek Drive
Libertyville, Illinois 60048(US)
Inventor: **Johnson, Edwin S.**
1037 Main Street
Antioch, Illinois 60002(US)

(74) Representative: **Modiano, Guido et al**
c/o Modiano & Associati S.r.l. Via Meravigli, 16
I-20123 Milano(IT)

(54) LHRH Analog formulations.

(57) The invention relates to novel suspension aerosol formulations comprising LHRH analogs.

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Technical Field

The invention relates to novel formulations comprising LHRH (luteinizing hormone releasing hormone) analogs and more particularly, to LHRH analog aerosol formulations.

Background Art

Polypeptides and LHRH analogs in particular are historically administered parenterally because they are poorly absorbed by biological membranes due to their large molecular size and polarity, enzymatic degradation and deactivation by proteases enroute to the circulatory system. To improve bioavailability, some have developed formulations for rectal and nasal administration.

Known in the art are nasal spray compositions with which an enhanced absorption of polypeptides and in particular LHRH analogs was attained using a chelating agent such as disodium EDTA in a buffered aqueous solution, as disclosed in US-A- 4476116 or using a surfactant which is a bile acid or a pharmaceutical acceptable salt thereof in a buffered aqueous solution, as disclosed in EP-A- 0 111 841.

To date no aerosol formulation has been developed for administration of LHRH analogs by inhalation. This is due in part because many peptide drugs such as LHRH agonist and antagonist compounds do not appreciably dissolve in hydrophobic liquid vehicles to enable preparation of solution aerosols. Further, since suspension aerosols require micronization of the LHRH analogs, usually in air for efficiency reasons, and the LHFH analogs are biologically hazardous in low concentrations, suspension aerosols of LHRH analogs have not been considered feasible.

For example, leuprolide is a polar nonapeptide with three ionizable sites, namely the imidazolyl nitrogen of histidine with pKa approximately 6.0, the phenolic hydroxyl of tyrosine with pKa approximately 10.0, and the guanidine nitrogen of arginine with pKa approximately 13.0. Since the guanidine nitrogen is extremely basic, this nonapeptide as synthesized exists in the protonated form and is generally associated with at least one mole of acetic acid. Leuprolide, therefore, exists as an acetate salt, which is highly hydrophilic.

LHRH analogs are practically insoluble in fluorocarbons. In mixtures of ethyl alcohol and fluorocarbons, the solubility of leuprolide approaches 3 mg/ml which is not satisfactory due to dose requirements. This solubility estimate is not significantly affected by the presence of nonionic surfactants because, in part, of solubility and dielectric limitations of such surfactants. In mixtures of fluorocarbons, ethyl alcohol and water, experimental results showed equilibrium solubility of leuprolide to approach 5 mg/ml which is still unacceptable. At high concentrations of ethyl. alcohol, a gel-like mass forms resulting in a colloidal dispersion that does not clear at room temperature for up to one month. At water concentrations of 10% or greater, a complete phase separation occurs making a homogeneous formulation impractical and renders aerosolization impractical.

Preparing suspension aerosols requires micronization of the drug prior to manufacture of the aerosol. This process involves mechanical breakup of the powder using grinding or milling equipment to reduce drug particle size to below 10 µm which is essential for pulmonary deposition of the aerosol. Generally, this milling process results in significant exposure of the drug to the surrounding environment as well as up to 20% loss of the drug. The airborne LHRH analog particles can cause safety and health hazards if precautionary measures are not taken.

Disclosure of the Invention

The technical and safety hazards associated with preparing suspension aerosols can be overcome by liquid milling LHRH analogs and using a low boiling liquid propellant. Bioavailability of leuprolide, a prototype peptide in this invention, ranges from 50% to 100% of the intravenously administered product as a control formulation. Time for plasma peak concentration to occur is about 30 minutes, and the plasma peak concentration itself approximately equals that of a comparable dose administered intravenously.

In particular, the solution aerosol formulations for administration of LHRH analogs comprise:

In particular, the suspension aerosol formulations for administration of LHRH analogs comprise:

1. LHRH analogs (active ingredient)
2. surfactant (dispersing agent)
3. solvent (Freon 11 and/or Absolute alcohol)
4. propellant and optionally
5. surfactant (wetting agent and valve lubricant)
6. antioxidant
7. flavor/fragrance.

Illustrative of such formulations are those comprising 0.01-5% w/w LHRH analog, 0.05-10% w/w surfactant, 0-55% w/w solvent and 30-99% w/w propellant.

The preferred suspension formulation of the invention is as follows:

Ingredient	Ranges
Trichlorofluoromethane	0.00 - 55.00% w/w
Sorbitantrioleate	0.05 - 10.00% w/w
Dichlorodifluoromethane	30.00 - 99.00% w/w
Leuprolide Acetate	0.01 - 5.00% w/w

Best Mode for Carrying Out the Invention

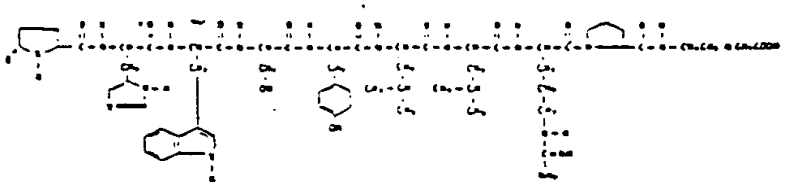
The suspension aerosol composition for administration of LHRH analogs comprises:

Ingredient	Range
Trichlorofluoromethane	0.00 - 550 mg/gm
Sorbitantrioleate	0.05 - 100 mg/gm
LHRH* Analog	0.01 - 50 mg/gm
Dichlorodifluoromethane	30.00 - 990 mg/gm

As used herein, "% w/w" refers to weight of ingredient per weight of formulation multiplied by 100.

As used herein, the term "LHRH analog" refers to octapeptides, nonapeptides and decapeptides including but not limited to leuprolide and D-amino acid analogs of LHRH. More particularly, LHRH analogs in addition to leuprolide (U.S. Patent No. 4,005,063) which can be formulated in accordance with the invention include those which are described in U.S. Patent Nos. 3,853,837, 3,972,859, 4,008,209, 4,024,248 (buserilin) 4,089,946 (lutrelin), 4,100,274 (goserelin), 4,234,571 (nafarelin), 4,490,291, and also includes histrelin.

As used herein, the term "leuprolide" or "leuprolide acetate" refers to a nonapeptide, 5-Oxo-L-prolyl-L-histidyl-L-tryptophanyl-L-seryl-L-tyrosyl-D-leucyl-L-leucyl-L-arginyl-L-prolylethylamide acetate with the structure:



As used herein, the term "surfactant" refers to nonionic surfactants including but not limited to mono and diglycerides, sorbitan fatty acid esters, polyoxyethylene sorbitan fatty acid esters, polyoxyethylene sorbitol esters, polyoxyethylene acid, polyoxyethylene alcohols and polyoxyethylene adducts.

As used herein, the tern "propellant" refers to chlorofluorocarbons or hydrocarbons including but not limited to trichlorofluoromethane, dichlorodifluoromethane, chlorodifluoromethane and dichlorotetrafluoroethane.

A preferred suspension aerosol contains approximately 10% w/w trichlorofluoromethane, 3% w/w sorbitan trioleate, 1.0% w/w leuprolide acetate, and 86% w/w dichlorodifluoromethane. This formulation has good spray characteristics and has satisfactory physical and chemical stability. This formulation can be prepared as follows:

a) Add the leuprolide and glass or tungsten beads to the milling chamber (Dyno Mill obtained from Glen Mills, Inc., Maywood, N.J.).

b) Add the trichlorofluoromethane and an appropriate amount of surfactant to the milling chamber.

c) Close milling chamber tightly, and begin to chill the slurry to approximately -20° C.

d) Mill the slurry by circulation either continuously or in batches until the particles are in the appropriate

respirable size range.
e) Empty the slurry into aerosol containers. Add propellant and crimp containers using either cold fill or pressure fill method.
f) Check for leaks in warm water bath.

Claims

1. A suspension aerosol formulation comprising an LHRH analog, surfactant, solvent and propellant.

2. The formulation of Claim 1 comprising 0.01-5% w/w LHRH analog, 0.05-10% w/w surfactant, 0-55% w/w solvent and 30-99% w/w propellant.

3. The formulation of Claim 2 wherein the LHRH analog is leuprolide acetate, the surfactant is sorbitan-trioleate, the solvent is trichlorofluoromethane and the propellant is dichlorodifluoromethane.

4. The formulation of Claim 3 consisting of 1% w/w leuprolide acetate, 3% w/w sorbitantrioleate, 10% w/w trichlorofluoromethane and 86% w/w dichlorodifluoromethane.

Claims for the following Contracting States : ES, GR

1. A process for preparing a suspension aerosol formulation comprising admixing an LHRH analog, surfactant, solvent and propellant.

2. The process of Claim 1 comprising admixing 0.01-5% w/w LHRH analog, 0.05-10% w/w surfactant, 0-55% w/w solvent and 30-99% w/w propellant.

3. The process of Claim 2 wherein the LHRH analog is leuprolide acetate, the surfactant is sorbitan-trioleate, the solvent is trichlorofluoromethane and the propellant is dichlorodifluoromethane.

4. The process of Claim 3 comprising admixing 1% w/w leuprolide acetate, 3% w/w sorbitantrioleate, 10% w/w trichlorofluoromethane and 86% w/w dichlorodifluoromethane.

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EUROPEAN SEARCH REPORT

Application Number

EP 92 11 1535

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.4)
Y	US-A-4 476 116 (ANIK) * column 1, line 6 - line 14 * * column 6, line 10 - column 8, line 60 * * column 10, line 45 - column 16, line 48 *	1-4	A61K9/72 A61K37/43
Y	EP-A-0 111 841 (SYNTEX (U.S.A.) INC.) * the whole document *	1-4	
Y	FR-A-2 205 307 (FARBWERKE HOECHST AG VORMALS MEISTER LUCIUS & BRÜNING) * page 6; example 11 * * claims 1-6 *	1-4	
Y	US-A-4 405 598 (BROWN) *column 9, examle 6, table b, formulations d, f*	1-4	
A	US-A-3 560 607 (HARTLEY) * column 4; example 5 * * claims 1-5 *	1-4	
A	JOURNAL OF PHARMACEUTICAL SCIENCES vol. 71, no. 12, December 1982, WASHINGTON (US) pages 1367 - 1371; H. OKADA ET AL.: 'vaginal absorption of a potent luteinizing hormone - releasing hormone analog (leuprolide) in rats I : absorption by various routes and absorption enhancement' * page 1367 *	1-4	TECHNICAL FIELDS SEARCHED (Int. Cl.4) A61K

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	14 AUGUST 1992	BENZ K.F.

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

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